L1: Entry 16 of 20 File: USPT Mar 2, 2004

DOCUMENT-IDENTIFIER: US 6699908 B2
TITLE: Methods for providing safe local anesthesia

Brief Summary Text (7):
Another approach was based on analysis of the structure-activity relationship of the local anesthetic compounds. Structure-activity analysis for local anesthetic compounds indicates that relative increases in hydrophobicity are accompanied by relative increases in the potency and in duration of action of these agents. Unfortunately, relative increases in hydrophobicity also elevate the toxic tissue effects, therefore resulting in no effective improvement in the therapeutic index, i.e., no increase in safety will result from this approach. The most recent example of this approach is Naropin.TM. (ropivacaine, Astra Pharmaceuticals), which was reported to be a safer (relative to bupivacaine solution) long acting amide local anesthetic for injection. However, one condition for the approval of ropivacaine is that the package insert warn against rapid injection in large doses, since it is expected to share the risk of cardiac arrhythmias, cardiac/circulatory arrests and death if inadvertently injected intravenously (F-D-C Reports--"The Pink Sheet", Dec. 18, 1995). Thus, there remains a need in the art for methods and formulations enhancing the safety of administration of local anesthetics.

Brief Summary Text (8):
Different methods and formulations are known in the art for administration of local anesthetics. For example, U.S. Pat. Nos. 4,725,442 and 4,622,219 (Haynes) are directed to microdroplets of methoxyflurane-containing microdroplets coated with a phospholipid prepared by sonication, which are suitable for intradermal or intravenous injection into a patient for inducing local anesthesia. Such microdroplets are said to provide long-term local anesthesia when injected intradermally, giving a duration of anesthesia considerably longer than the longest acting conventional local anesthetic (bupivacaine).

5,202,119
6022711
HGH by Bolus
5,843,422
5,187,157
GH
= HGH
6274175
5817773

L7: Entry 100 of 228 File: USPT Oct 1, 2002

DOCUMENT-IDENTIFIER: US 6458360 B1
TITLE: Soluble complement regulatory molecules

Detailed Description Text (32):
The carrier is a macromolecule which is soluble in the circulatory system and which is physiologically acceptable where physiological acceptance means that those of skill in the art would accept injection of said carrier into a patient as part of a therapeutic regime. The carrier preferably is relatively stable in the circulatory system with an acceptable plasma half-life for clearance. Suitable carriers include, but are not limited to, proteins such as serum albumin, heparin, or immunoglobulin, polymers such as polyethylene glycol or polyoxyethylated polyols, or proteins modified to reduce antigenicity by, for example, derivitizing with polyethylene glycol. Suitable carriers are known in the art and are described, for example, in U.S. Pat. Nos. 4,745,180, 4,766,106 and 4,847,325 and references cited therein.

Detailed Description Text (49):
In the above method, the compounds may be administered by any convenient route, for example by infusion or bolus injection. Various delivery systems are known and can be used for deliver of fusion proteins and constructs. These include encapsulation in liposomes, microparticles, or microcapsules. Other methods of introduction include but are not limited to intradermal, intramuscular, intrapertioneal, intravenous, subcutaneous, intranasal, and oral routes.

CLAIMS:

4. The soluble construct according to claim 1, wherein the carrier molecule is selected from the group consisting of: serum albumin, heparin, immunoglobulin, polyethylene glycol, and polyoxyethylated polyols.

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L7: Entry 141 of 228 File: USPT Oct 30, 2001

DOCUMENT-IDENTIFIER: US 6309826 B1
TITLE: 88kDa tumorigenic growth factor and antagonists

Detailed Description Text (28):
According to the present invention, antibodies that neutralize GP88 activity in vitro can be used to neutralize GP88 activity in vivo to treat diseases associated with increased GP88 expression or increased responsiveness to GP88, such as but not limited to cancer and viral infection. A subject, preferably a human subject, suffering from disease associated with increased GP88 expression is treated with an antibody to GP85. Such treatment may be performed in conjunction with other anti-cancer or anti-viral therapy. A typical regimen comprises administration of an effective amount of the antibody specific for GP88 administered over a period of one or several weeks and including between about one and six months. The antibody of the present invention may be administered by any means that achieves its intended purpose. For example, administration may be by various routes including but not limited to subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal and oral. Parenteral administration can be by bolus injection or by gradual perfusion over time. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions, which may contain auxiliary agents or excipients known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to routine methods. It is understood that the dosage of will be dependent upon the age, sex and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. The ranges of effective doses provided below are not intended to limit the invention and merely represent preferred dose ranges. However the most preferred dosage will be tailored to the individual subject as is understood and determinable by one skilled in the art. The total dose required for each treatment may be administered by multiple doses or in a single dose. Effective amounts of antibody are from about 0.01 .mu.g to about 100 mg/kg body weight and preferably from about 10 .mu.g to about 50 mg/kg. Antibody may be administered alone or in conjunction with other therapeutics directed to the same disease.

Detailed Description Text (111):
For recombinant GP88 production, the method of choice was to express GP88 in the baculovirus system. A full length GP88 cDNA (obtained by screening PC cell cDNA library) including the signal peptide was ligated into the baculoviuus transfer vector pVL1392 (in Vitrogen, San Diego, Calif.). Plasmid pVL1392-GP88 was used to co-transfect Sf9 insect cells with baculovirus DNA. Recombinant viruses encoding GP88 were isolated and plaque purified. For infection and production of recombinant GP88, Sf9 cells were seeded in Grace's medium containing 10% fetal bovine serum (FBS) in T75 cm.sup.2 flasks. After infection with recombinant baculovirus-GP88, insect cells were maintained in Grace's medium for 48 hours at 27.degree. C. Conditioned medium was collected by centrifugation and recombinant GP88 (rGP88) was purified by a 2 step purification protocol consisting of heparin-sepharose and immunoaffinty chromatography as described in Example 6. SDS-PAGE analysis of rGP88 indicated that rGP88 migrates faster than PC cell derived GP88 corresponding to an apparent MW of 76 kDa. N-terminal sequencing analysis of rGP88 indicated that it was identical to GP88 purified from PC-CM. The difference of molecular weight between GP88 and rGP88 is due to a difference in glycosylation status of GP88 in

insect cells. As shown in FIG. 6, biological activity of rGP88 was identical to that of GP88 purified from PC cells, indicating that the different glycosylation status of GP88 in insect cells and mammalian cells did not affect the biological potency of the protein.

Detailed Description Text (115):
The conditioned medium (2000 ml) from PC cells was diluted with the same volume of H.sub.2 O and loaded on a 2.5 ml heparin-sepharose CL-6B column equilibrated in 10 mM sodium phosphate buffer pH 7.4 containing 75 mM NaCl (Pharmacia, Uppsala, Sweden). The column was washed with at least 10 bed volumes of the same equilibration buffer followed by a wash with 10 mM sodium phosphate buffer containing 0.15 M NaCl. The fraction containing GP88 was eluted with 5 bed volumes of 0.4 M NaCl, 10 mM Tris-HCl, pH 7.5. The eluate was stored at -20 .degree. C. for further purification. A synthetic peptide K19T (SEQ ID NO: 3) (sequence: KKVIAPRRLPDPQILKSDT) was used to raise the antisera against the GP88 used in the immunoaffinity step. The K19T peptide was linked to CNBr-activated Sepharose 4B according to the method provided by the manufacturer (Pharmacia, Uppsala, Sweden). The specific anti-K19 antibody was purified using the K19T peptide affinity column by elution at acidic pH. Specifically, anti-K19T IgG was applied to a K19T peptide-Sepharose 4B column equilibrated with 10 mM sodium phosphate buffer pH 6.5 (Buffer A) at a flow rate of 0.8 ml/hr, and circulated at 4.degree. C. overnight. After washing the column with 7 ml of Buffer A, the conjugate was eluted with 1 ml of HCl, pH 2.9, then 1 ml of HCl, pH 2.5 at a flow rate of about 0.1 ml/min in a tube containing 0 1 ml of 1M sodium phosphate buffer pH 7.0 to neutralize the pH. The concentration of affinity-purified IgG was determined by the absorbance at 280 nm.

Detailed Description Text (116):
The purified Ab-K19T (1 mg) was then conjugated to 1 ml of agarose beads (Sulfolink coupling gel, Pierce, Rockford, Ill.) using protocols provided by the manufacturer. The final coupled column contained 600 .mu.g anti-K19T/ml gel. The Ab-K19T agarose was packed in a column and washed extensively with PBS. The eluate from heparin sepharose CL-6B column was diluted with 3 volumes H.sub.2 O and loaded on the Ab-K19T column. After washing the column with buffer consisting of 750 mM NaCl in 10 mM NaPO4 pH 7.5, the fraction containing GP88 was eluted by elution buffer (150 mM NaCl, pH 2.5 (HCl)). To neutralize, 1/10 volume (v/v) 1 M sodium phosphate pH 6.5 buffer was added to the eluate and the protein concentration was determined by amino acid analysis or micro BCA kit (Bio-Rad, Richmond, Calif.). In general 50 .mu.g of GP88 was purified on a 350 .mu.l column.

Detailed Description Text (134):
A 228 bp fragment of GP88 cDNA was cloned in the antisense orientation in pCMV4 expression vector (Andersson, S., et al, 1989) (51) containing CMV promoter and hGH transcription termination and polyadenylation signals (pCMV4-GP88AS). PC cells were co-transfected with the 20 .mu.g of antisense pCMV4GP88AS and 2 .mu.g of pRSVneo expression vector containing the neomycin resistant gene by the calcium phosphate method. Control cells were co-transfected with empty pCMV4 vector and pRSVneo as described above. Transfected cells were selected in the presence of neomycin. Neomycin resistant colonies were cloned and cells were assayed first by detecting the presence of pCMV4GP88AS by PCR. Twenty-four positive neomycin resistant clones containing the antisense pCMV4GP88AS were isolated. Nine have been isolated and screened for expression of the antisense transcript. Three clones were further characterized. Western blot analysis of cell lysates and conditioned medium using anti-GP88 antiserum (i.e., anti-K19T antibody) was performed in order to determine the level of GP88 expression in transfected antisense cells and control cells (FIG. 7). Culture medium and cell lysates were prepared by immunoprecipitation with anti-K19T antibody. Protein samples corresponding to 3.times.10.sup.6 cells/lane were analyzed by Western blotting with anti-GP88 antibody. The results indicate that GP88 levels are significantly lower in antisense, than in control, transfected cells particularly for AS1 and AS18 clones.

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Detailed Description Text (214):
8) Adelman, J P, Hayflick, J S, Vasser, M, Seeburg, P H (1983) In vitro deletional mutagenesis for bacterial production of the 20,000 dalton form of human pituitary growth hormone. DNA, 2, 183-193.

Other Reference Publication (17):
In Vitro Deletional Mutagenesis for Bacterial Production of the 20,000-Dalton Form of Human Pituitary Growth Hormone, Adelman, J. et al., DNA, vol. 2, No. 3, 1983, pp. 183-193.

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L7: Entry 146 of 228 File: USPT Aug 14, 2001

DOCUMENT-IDENTIFIER: US 6274175 B1
TITLE: Prolonged release of GM-CSF

Drawing Description Text (5):
FIG. 2B is a graph of mouse serum GM-CSF levels (ng/ml) over time (days) following microsphere or bolus injections, for 50 mg microspheres, 500 .mu.g bolus, and 50 .mu.g bolus.

Detailed Description Text (44):
Degradation enhancers are based on weight relative to the polymer weight. They can be added to the protein phase, added as a separate phase (i.e., as particulates) or can be codissolved in the polymer phase depending on the compound. In all cases the amount should be between 0.1 and thirty percent (w/w, polymer). Types of degradation enhancers include inorganic acids such as ammonium sulfate and ammonium chloride, organic acids such as citric acid, benzoic acids, heparin, and ascorbic acid, inorganic bases such as sodium carbonate, potassium carbonate, calcium carbonate, zinc carbonate, and zinc hydroxide, and organic bases such as protamine sulfate, spermine, choline, ethanolamine, diethanolamine, and triethanolamine and surfactants such as Tween.TM. and Pluronic.TM..

Detailed Description Text (47):
Stabilizers for the GM-CSF are based on the ratio by weight of stabilizer to the GM F on a weight basis. Examples include carbohydrate such as sucrose, lactose, manitol, dextran, and heparin, proteins such as albumin and protaiine, amino acids such as arginine, glycine, and threonine, surfactants such as Tween.TM. and Pluronic.TM., salts such as calcium chloride and sodium phosphate, and lipids such as fatty acids, phospholipids, and bile salts.

Detailed Description Text (114):
Release studies were conducted on mice as follows. Male B6 mice (6 weeks old) were obtained from Jackson Laboratories (Bar Harbor, Me.) and were housed in the Immunex animal laboratory facility for an additional 10 weeks prior to initiating the study. Seventeen groups of mice were used in the study, with three mice used per group. For the test group 50 mg of microspheres containing 500 .mu.g of huGM-CSF (1% by wt) were injected subcutaneously in 0.5 ml of the methyl cellulose injection vehicle. Groups of mice receiving these injections were sacrificed at intervals of 1, 2, 6, 24 hr, 3, 5, 7, and 9 days. As a negative control, one group of mice was sacrificed without receiving huGM-CSF in any form. As a final control a bolus of huGM-CSF was injected subcutaneously at a dose of either 500 or 50 .mu.g of huGM-CSF. The 500 .mu.g dose represented the entire amount of huGM-CSF contained in a 50 mg injection of microspheres, and the 50 .mu.g dose represented an approximation of the amount of huGM-CSF released by 50 mg of microspheres over a period of 1 day in vitro. Groups of mice receiving bolus injections were sacrificed at intervals of 1, 2, 6, and 24 hr post-injection.

Detailed Description Text (121):
Results of the release study are shown in FIG. 2A, which is a graph of the in vitro release kinetics showing release over a period of about ten days. FIG. 2B is a graph of the circulating mouse serum huGM-CSF levels (determined by ELISA) as a function of time. Both the 500 and 50 .mu.g bolus injections were rapidly cleared

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from mouse serum. Due to the rapid decline of detectable huGM-CSF in mouse serum only a rough estimate of the .beta. elimination half-life could be made (t.sub.1/2.beta.=1.57 hr); however, this estimate agrees closely with previously reported half-lives for huGM-CSF circulating in a mouse model. Levels of serum huGM-CSF in the mice which received microspheres dropped rapidly over the first 6 hours post-injection (from 218 to 5 to 35 ng/ml), and then remained relatively constant over the remaining 9 days of the study. Presumably, given the in vitro release profile for this lot of microspheres (approximately 30% release after 9 days) huGM-CSF would have released from the microspheres beyond the 9 day period where the in vivo study was terminated.

Detailed Description Paragraph Table (1):
TABLE 1 In Vivo Microsphere Release Study Outline Post-Injection Group Description Sacrifice Time 1 no injection, negative control 0 hr 2 500 .mu.g huGM-CSF bolus injection 1 hr 3 50 .mu.g huGM-CSF bolus injection 1 hr 4 50 mg microspheres injected 1 hr 5 500 .mu.g huGM-CSF bolus injection 2 hr 6 50 .mu.g huGM-CSF bolus injection 2 hr 7 50 mg microspheres injected 2 hr 8 500 .mu.g huGM-CSF bolus injection 6 hr 9 50 .mu.g huGM-CSF bolus injection 6 hr 10 50 mg microspheres injected 6 hr 11 500 .mu.g huGM-CSF bolus injection 24 hr 12 50 .mu.g huGM-CSF bolus injection 24 hr 13 50 mg microspheres injection 24 hr 14 50 mg microspheres injected 72 hr (3 day) 15 50 mg microspheres injected 120 hr (5 day) 16 50 mg microspheres injected 168 hr (7 day) 17 50 mg microspheres injected 216 hr (9 day)

Other Reference Publication (22):
Kaplan G., et al., "Novel Responses of Human Skin to Intradermal Recombinant Granulocyte/Macrophage-Colony Stimulating Factor: Langerhans Cell Recruitment, Keratinocyte Growth, and Enhanced Wound Healing," J. Exp. Med. 175:1717-1728 (1992).

Other Reference Publication (46):
Mitsuyasu R., Clinical Uses of Hematopoietic Growth Hormones in HIV-Related Illnesses, AIDS Clin. Rev. 196-204, (1993/1994).

L7: Entry 200 of 228 File: USPT Oct 20, 1998

DOCUMENT-IDENTIFIER: US 5824781 A
TITLE: Compositions and methods utilizing nitroxides in combination with biocompatible macromolecules

Detailed Description Text (52):
With respect to selecting a particular formulation and method of administration pursuant to this invention, the formulation and method of administration are dictated by the particular application. The selection of a nitroxide-based compound capable of accepting an electron from a low molecular weight membrane permeable species for a particular application may be made to complement, several available methods of administration and preferred formulations may be selected based on the site specific protection desired for the particular application. The avoidance of oxidative stress from infusion of a hemoglobin-based oxygen carrier as described above is a prime example of selecting formulations and methods of administration pursuant to this invention to provide specific protection from free radical toxicity to avoid the toxic side effects of HBOC infusion. Where site specific protection or activity is desired in the skin or dermal layers a preferred compound is TOPS because it is relatively small and membrane permeable. Where specific protection or activity is desired in the gastrointestinal tract, a polynitroxide dextran is preferred because such a compound is less susceptible to enzymatic digestion while in the gastrointestinal tract. In such an application, oral or rectal administration is preferred. Where specific protection or activity is sought for the intravenous or intravascular regions, such as the cardiovascular system, a polynitroxide albumin is preferred because albumin is a major plasma protein, is well-tolerated, easy to administer, and exhibits an extended plasma half-life. Such application may include a hemoglobin-based oxygen carrier or polynitroxide derivative thereof. The same rationale applies for intraperitoneal or intradermal administration. If specific protection in the lungs is desired, an aerosol form of polynitroxide albumin is preferred to enable coating of the pulmonary airways. As will be apparent to those skilled in the art, these preferred formulations may be altered depending on the particular application.

Detailed Description Text (85):
Referring to FIG. 7A, 7B, and 7C the .sup.15 ND.sub.17 -TEMPOL signal could not be detected, however, the 4-(2-bromoacetamido)-TEMPO-labelled HBOC was clearly resolved (see FIG. 7B and 7C for plasma half-life studies where 7C is a continuation of 7B). Since the vasoconstrictive effect of HBOC is reported to be fully developed during the first 5-15 minutes of bolus injection of an HBOC in rats, the participation of the nitroxide-labelled HBOC in free radical redox-reactions immediately after transfusion in a mouse was measured. The tail vein of female CH3 mouse was cannulated under anesthesia with 80% nitrous oxide, 20% oxygen, and 3% isofluorane. Under a heat lamp the mouse tail vein became visibly distended, a cannula consisting of a 30 gauge hypodermic needle attached to a one foot length of polyethylene tubing was inserted into the tail vein and held in place by cyanoacrylate glue. For in vivo ESR measurements, the cannulated mouse was transferred under anesthesia to a 50 ml conical centrifuge tube modified to allow the tail to protrude from the conical end and to allow a continuous flow of anesthetic gas from the opening end of the tube. The tail was inserted into a plastic tube which was then fitted into a TE 102 cavity. The cannula was flushed periodically with heparin (100 unit/ml) to ensure patency. The cannula was near the

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root of the tail and was kept outside of the ESR cavity so that a pure signal from the tail could be measured immediately after bolus injection. 0.5 ml of samples (see FIG. 8) were injected via the cannula and the spectrometer was set for a repeat scanning mode at 1/2 min. intervals (see FIGS. 8A and 8B). In FIG. 8A the magnetic field was increased by two Gauss, and in FIG. 82 the magnetic field was decreased by two Gauss, to superimpose the resonance spectra. The .sup.15 ND.sub.17 -TEMPOL signal disappeared within 2.5 minutes after injection. During the same time period the 4-(2-bromoacetamido)-TEMPOL-labelled HBOC also decreased at a similar rate.

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L7: Entry 199 of 228 File: USPT Nov 3, 1998

DOCUMENT-IDENTIFIER: US 5830478 A
TITLE: Method for delivering functional domains of diphtheria toxin to a cellular target

Detailed Description Text (6):
DT is a single chain polypeptide comprised of 535 amino acid residues. Its crystal structure depicts three physical domains which correlate closely with its three functional activities, receptor binding (R), translocating (T) and catalytic (C) (FIG. 1). The C domain comprises amino acids 1-193, the T domain comprises amino acids 194-386 and the R domain comprises amino acids 387-535. The cell-surface receptor used by DT is an integral membrane protein that has been cloned and identified as a heparin-binding EGF-like growth factor precursor.

Detailed Description Text (28):
The compositions described herein (i.e., hybrid reagents and moieties) can be administered to a host in a variety of ways. The routes of administration include intradermal, transdermal (e.g., slow release polymers), intramuscular, intraperitoneal, intravenous, subcutaneous, oral, epidural and intranasal routes. Any other convenient route of administration can be used, for example, infusion or bolus injection, or absorption through epithelial or mucocutaneous linings. In addition, the reagents and moieties of the invention can be administered with other components or biologically active agents, such as pharmaceutically acceptable surfactants (e.g., glycerides), excipients (e.g., lactose), carriers, diluents and vehicles. If desired, certain sweetening, flavoring and/or coloring agents can also be added. The hybrid reagents and moieties can be administered prophylactically or therapeutically to a host and can result in amelioration of, or elimination of a disease state (e.g., cancer).

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L7: Entry 207 of 228 File: USPT Jun 23, 1998

US-PAT-NO: 5770623
DOCUMENT-IDENTIFIER: US 5770623 A
**** See image for Certificate of Correction ****

TITLE: Argine antagonists for inhibition of systemic hypotension associated with nitric oxide production or endothelial derived relaxing factor

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kilbourn; Robert G.	Naperville	IL		
Gross; Steven S.	New York	NY		
Levi; Roberto	New York	NY		
Griffith; Owen W.	Milwaukee	WI		

US-CL-CURRENT: 514/565; 424/85.1, 424/85.2, 424/85.5, 514/12, 514/930

CLAIMS:

What is claimed is:

1. A method for treating toxicity in a patient caused by excess levels of nitric oxide, the method comprising administering a therapeutically effective amount of a nitric oxide synthesis inhibitor to said patient.

2. The method of claim 1 where the toxicity is septic shock.

3. A method for the treatment of septic shock in a patient caused by excess levels of nitric oxide, the method comprising administering a therapeutically effective amount of a nitric oxide synthesis inhibitor to said patient.

4. A method for the inhibition of nitric oxide production in a patient having septic shock, the method comprising administering a therapeutically effective amount of a nitric oxide synthesis inhibitor to said patient.

5. A method for treatment of systemic hypotension in a patient having septic shock, caused by excess nitric oxide production comprising administering a therapeutically effective amount of a nitric oxide synthesis inhibitor to said patient.

6. The method of claim 5 where the nitric oxide production is induced by a cytokine.

7. A method for treatment of a patient having systemic hypotension induced by chemotherapeutic

treatment with a cytokine comprising administering a therapeutically effective amount of a nitric oxide synthesis inhibitor.

8. The method of claim 6 or 7 where the cytokine is at least one of gamma interferon, interleukin-1, and interleukin-2.

9. The method of claim 6 or 7 where the cytokine is tumor necrosis factor.

10. A method for the treatment of a patient having systemic hypotension induced by endotoxin comprising administering a therapeutically effective amount of a nitric oxide synthesis inhibitor.

11. A method for prophylaxis or treatment of systemic hypotension in a patient caused by nitric oxide production induced by at least one cytokine selected from the group consisting of gamma interferon, interleukin-1, and interleukin-2 comprising administering an amount of a nitric oxide synthesis inhibitor sufficient to elevate blood pressure.

12. A method for prophylaxis or treatment of systemic hypotension in a patient caused by nitric oxide production induced by tumor necrosis factor comprising administering an amount of a nitric oxide synthesis inhibitor sufficient to elevate blood pressure.

13. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 where the nitric oxide synthesis inhibitor is an arginine analog.

14. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 where the nitric oxide synthesis inhibitor is nitro-L-arginine methyl ester.

15. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 where the nitric oxide synthesis inhibitor is a competitive inhibitor of nitric oxide synthase.

16. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 where the nitric oxide synthesis inhibitor is an N.sup.G substituted arginine or an N.sup.G,N.sup.G -disubstituted arginine.

17. The method of claim 16 wherein the N.sup.G -substituted or N.sup.G,N-disubstituted arginine has a nitro, amino, lower alkyl, lower hydroxyalkyl, carboxyalkyl, aminoalkyl or alkenyl substituent replacing a hydrogen of a guanidino amino group.

18. The method of claim 16 wherein the N.sup.G -substituted arginine is N.sup.G -arginine is N.sup.G -nitroarginine, N.sup.G methylarginine, N.sup.G -ethylarginine or N.sup.G -propylarginine.

19. The method of claim 16 wherein the N.sup.G -substituted arginine is N.sup.G -methyl-L-arginine.

20. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 wherein said therapeutically effective amount of a nitric oxide synthesis inhibitor inhibits production of nitric oxide from arginine.

21. The method of claim 20 where the therapeutically effective amount is from 0.1 to 100 mg/kg body weight.

22. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 wherein the administering is intravascular.

23. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 wherein the administering is parenteral.

24. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 wherein the administering is enteral.

25. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 wherein the administering is intraperitoneal, intramuscular, intradermal or topical.

L7: Entry 213 of 228 File: USPT Jun 17, 1997

DOCUMENT-IDENTIFIER: US 5639473 A
TITLE: Methods for the preparation of nucleic acids for in vivo delivery

Brief Summary Text (6):
Pharmaceuticals that are water-insoluble or poorly water-soluble and sensitive to acid environments in the stomach cannot be conventionally administered (e.g., by intravenous injection or oral administration). The parenteral administration of such pharmaceuticals has been achieved by emulsification of oil solubilized drug with an aqueous liquid (such as normal saline) in the presence of surfactants or emulsion stabilizers to produce stable microemulsions. These emulsions may be injected intravenously, provided the components of the emulsion are pharmacologically inert. For example, U.S. Pat. No. 4,073,943 describes the administration of water-insoluble pharmacologically active agents dissolved in oils and emulsified with water in the presence of surfactants such as egg phosphatides, pluronics (copolymers of polypropylene glycol and polyethylene glycol), polyglycerol oleate, etc. PCT International Publication No. WO85/00011 describes pharmaceutical microdroplets of an anaesthetic coated with a phospholipid, such as dimyristoyl phosphatidylcholine, having suitable dimensions for intradermal or intravenous injection.

Detailed Description Text (310):
Anesthetized Sprague-Dawley rats (350-400 g) are catheterized through the external jugular vein. A bolus injection of an iso-oncotic suspension of IHC equivalent to 20% of the animals' blood volume is given through the catheter. Blood is withdrawn at sampling times ranging from 0.25 to 92 hours. Blood samples are centrifuged and plasma observed for signs of hemolysis or presence of soluble hemoglobin. Since the `microbubbles` of the IHC have a gaseous interior (and are therefore of lower density than water), they rise to the surface of the plasma following centrifugation. The microbubbles are skimmed off, resuspended in saline and counted in a particle counter. The half-lives of IHC in circulation is then determined. Compared to prior art hemoglobin-based blood substitutes, it is expected that invention IHC will demonstrate enhanced circulation half life.

CLAIMS:

8. The method according to claim 3, wherein said polysaccharides are selected from alginate, high M-content alginates, polymannuronic acid, polymannuronates, hyaluronic acid, hyaluronate, heparin, dextran, chitosan, chitin, cellulose, starch, glycogen, guar gum, locust bean gum, dextran, levan, inulin, cyclodextrin, agarose, xanthan gum, carrageenan, heparin, pectin, gellan gum, scleroglucan, or combinations of any two or more thereof.

L9: Entry 1 of 1 File: USPT Sep 25, 1990

DOCUMENT-IDENTIFIER: US 4959353 A
TITLE: Promotion of corneal stroma wound healing with human epidermal growth factor prepared from recombinant DNA

Brief Summary Text (11):
Methods and compositions for treating epithelial and stromal wounds to promote their rapid healing are provided. The method utilizes a treatment composition including a purified polypeptide having mitogenic activity capable of promoting the growth of both the epidermal and dermal layers of the skin as well as the epithelial and stromal layers of the cornea and other organs. Healing occurs, in part, as a result of the migration and multiplication of epithelial and stromal cells into the wound. The polypeptide is produced by recombinant DNA techniques, typically utilizing a synthetic gene having a nucleotide sequence based on the known amino acid sequence of human epidermal growth factor (hEGF). The compositions are applied topically to the affected area and include suitable carriers or bases. For general treatment of areas other than the cornea, the carrier will usually be an ointment or a cream, typically including an antibacterial agent. For corneal treatment, the carrier will be a suitable liquid or ointment.

Detailed Description Text (29):
Each animal was housed separately, and ten days post-incision the animals were sacrificed in a CO.sub.2 chamber. The wounds were entirely excised with the panniculus carnosus in a 3 cm.times.3 cm rectangle. Those animals in group A had no evidence of the incision when viewed dermal-side up. The animals in group B, however, has a visible defect remaining where the incision was placed when viewed dermal-side up. Burst strength measurement and hydroxyproline assays were all higher in the animals in group A than those in group B. These data indicate that hEGF enhances collagen synthesis as well as epithelialization, and, therefore, is potentially applicable in the treatment of many different types of surgical incisions.

Detailed Description Text (46):
Interscapular incisions were created as above on the backs of 22 rats and a perforated catheter was placed in the base of the incision and brought out through a separate stab incision at the base of the neck. Incisions of half the rats were treated three times a day for five days by rapidly injecting 200 .mu.l of PBS containing 50 .mu.g of hEGF, while the control rats received injections of PBS. Seven and 14 days after surgery, rats were sacrificed by carbon dioxide asphixiation, incisions and surrounding tissue were removed as above. Three strips were taken from tensile strength measurement from each incision.

L7: Entry 205 of 228 File: USPT Sep 1, 1998

DOCUMENT-IDENTIFIER: US 5800820 A
TITLE: Methods and compositions for treatment of angiogenic diseases

Brief Summary Text (8):
The mechanism of angiogenesis and endothelial cell proliferation has not been completely characterized. It has been established that mast cells accumulate at a tumor site before new capillary growth occurs; however, mast cells alone cannot initiate angiogenesis. Heparin, a mast cell product, has been shown to significantly stimulate the capillary endothelial cell migration which is necessary for angiogenesis (Folkman, J. [1984] Angiogenesis: Initiation and Modulation. In Cancer Invasion and Metastasis: Biologic and Therapeutic Aspects. G. L. Nicolson and L. Milas, eds. Raven Press, N.Y., pp. 201-208).

Brief Summary Text (9):
Several substances are known to have the capability of inhibiting endothelial cell growth in vitro. One of the most extensively studied inhibitors of endothelial cell growth is protamine, which is a protein found only in sperm. Protamine has been shown to inhibit tumor angiogenesis and subsequent tumor growth (Taylor, S. and J. Folkman [1982] Nature 297:307-312). Protamine's anti-angiogenesis activity has been attributed to its well-known capacity to bind heparin (Taylor and Folkman [1982], supra). Clinical experiments with protamine have not been pursued because of the toxicity associated with protamine injection. Protamine, which is usually isolated from salmon sperm, is known to be antigenic in humans, and anaphylactic reactions to this protein have been observed with secondary exposures.

Brief Summary Text (10):
At least two other compounds have been studied in regard to their heparin-binding activity: platelet factor 4 (PF4) and major basic protein. Major basic protein has demonstrated heparin-binding activity but is of little practical utility because of its high toxicity.

Brief Summary Text (11):
Platelet factor 4 is a well-known protein which has been completely sequenced (Deuel, T. F., R. M. Senior, D. Chang, G. L. Griffin, R. L. Heinrikson, and E. T. Kaiser [1981] Proc. Natl. Acad. Sci. USA 78:4585-4587). It is a 70-residue secretable platelet protein with a molecular weight of approximately 7.8 Kd which is released during platelet aggregation. Although there is evidence of heparin binding activity and some indications of anti-angiogenesis activity (Folkman [1984], supra), PF4 has never been shown to have clinical utility.

Detailed Description Text (4):
Treatment of the tumors and diseases described above can be either systemic, regional, or local (intralesional), depending upon the type and severity of the disease as well as the accessibility of the disease site. Systemic treatment includes intravenous bolus injections and infusions, subcutaneous injections, implants, refillable reservoirs and sustained release depots and intramuscular injections. As will be explained in more detail below, the inventors have discovered that effective anti-tumor dosages useful in systemic administration must be very high; these unusually high dosages, which are necessary for maximum efficacy, can be administered with acceptably low attendant toxicity. Regional

treatment includes intraarterial for the treatment of primary liver tumors and liver metastases, and for the treatment of kidney, brain and pancreatic tumors. Regional intraperitoneal treatment can be used for the treatment of tumors of the ovary. Local treatment can be used for tumors of the brain, uterus, bladder, head and neck, for Kaposi's sarcoma and other nonmetastatic skin cancers, for metastatic skin cancer once dissemination precludes further surgical excision, and for colon and rectal cancer.

Detailed Description Text (9):
The activity of the C-13 peptide is especially surprising in light of its inability to affect the anticoagulant activity of heparin. The use of the C-13 peptide offers several advantages over whole rPF4 such as reduced dosage (weight basis), reduced likelihood of antigenicity, and greater likelihood of effectiveness in novel dosage forms.

Detailed Description Text (10):
The C-13 peptide of PF4 also retains the ability to prevent Con-A induced immunosuppression in mice, an activity which is unaffected by heparin and probably independent of the ability of the peptide to inhibit angiogenesis.

Detailed Description Text (12):
The fact that the C-13 peptide inhibits angiogenesis without affecting the anticoagulant activity of heparin demonstrates that this small peptide would also have the benefit of not interfering with concurrent anticoagulant therapy. Additionally, small peptides are generally less antigenic than larger proteins, and, thus, the PF4 fragments can be used advantageously for oral and transdermal administration. These types of delivery are particularly useful in the treatment of gastrointestinal capillary proliferation (e.g., Kaposi's Sarcoma) and skin lesions, respectively. Intralesional, as well as systemic, administration of PF4 fragments are also appropriate for treatment of these conditions.

Detailed Description Text (13):
Analogs of PF4 were created which lack heparin binding activity but retain ability to inhibit angiogenesis. One such analog, known as rPF4-241, was created by cassette mutagenesis of a synthetic PF4 gene whereby the DNA sequence encoding the four lysine residues near the carboxy terminus of PF4 were converted to a sequence encoding two Gln-Glu couplets. If rPF4-241 is administered intralesionally, it can be applied such that the dosage is between about 1 .mu.g/lesion and about 4 mg/lesion. For systemic administration, the dosage of rPF4-241 can be between 0.5 mg/kg of body weight and about 100 mg/kg of body weight. Similar and higher dosages can be used for the administration of native sequence rPF4 as well as peptide fragments. For example, dosages of rPF4 and fragments thereof may be twice that of rPF4-241 or higher.

Detailed Description Text (18):
Endothelial Cell Proliferation Assay. Human umbilical vein endothelial cells (HUVEC) were cultured in Medium 199 (Gibco) containing 10% (v/v) fetal bovine serum (FBS), 150 mcg/ml endothelial cell growth supplement (ECGS) and 5 units/ml heparin at 37.degree. C. and 4-5% CO.sub.2. Every 3-4 days, the cultures were harvested by trypsin treatment, diluted, replated, and grown to confluence. Prior to the start of an experiment, the cells were centrifuged and resuspended in heparin-free media and incubated with the test substance (PF4) for 3 days under standard culture conditions. At the end of the incubation period, the cells were removed by trypsin treatment and counted with a Particle Data Elzone 180 Cell Counter. Statistical significance between means was determined by a standard Student t-test for unpaired data.

Detailed Description Text (25):
Cells expressing the fusion protein were subjected to lysozyme (1 mg/g cells), DNase I (500 units/100 g cells) and bead mill treatments. The lysis pellet

containing the fusion protein was treated with CNBr (10 g/100 g cells) in 70% formic acid to cleave the fusion protein at the methionine between the BG and PF4 portions. Following evaporation of the CNBr/formic acid, the recombinant protein was extracted with 200 ml of 50 mM Tris-Cl, pH 7.6, 5 mM EDTA, and 10 mM DTT per 100 g of cell starting material. Native sequence rPF4-211 was purified by binding the protein to heparin agarose, removing contaminating proteins with 0.6M NaCl, and eluting with 1.2M NaCl. The resulting material was dialyzed into 20 mM sodium acetate, pH 4.0, and analyzed on a 15% SDS-PA gel stained with Coomassie Brilliant Blue. Minor contaminants could be removed using C.sub.4 reverse phase high pressure liquid chromatography (HPLC) to prepare the protein for in vivo use.

Detailed Description Text (35):
The lysine rich region of PF4 (residues 61-66) is also the domain associated with the binding of heparin by PF4. Heparin is known to play a role in modulating angiogenesis, which can also be affected by protamine, another well characterized heparin-binding protein. To assess the ability of PF4-based synthetic peptides to bind heparin, we assayed the activity of coagulation-cascade enzymes which are inhibited by heparin. The Factor Xa assay used here has previously been described in Denton et al. (1983) Biochem. J. 209:455-460. Protamine and platelet factor 4 are able to prevent the heparin inhibition of thrombin and Factor Xa at approximately equimolar concentrations. The 41 amino acid C-terminal peptide of PF4 (C-41) prevented heparin inhibition less effectively, but the C-13 peptide was unable to prevent the inhibition of thrombin even at concentrations ten times that of an effective level of rPF4. This unexpected finding suggests that the C-13 peptide inhibits angiogenesis by some method other than heparin binding.

Detailed Description Text (37):
Many angiostatic agents act by direct inhibition of endothelial cell proliferation. Endothelial cell division and growth is tightly controlled and strictly dependent on the presence of growth factors. We evaluated the ability of rPF4 having the wild type sequence (rPF4-211) and related peptides to inhibit growth factor-stimulated human endothelial cell proliferation in vitro. As shown in FIG. 3, rPF4 significantly inhibited endothelial cell growth in a dose-dependent fashion at a concentration as low as 1.3 .mu.M. Inhibition was complete at 3.2 .mu.M in the heparin-deficient medium employed here.

Detailed Description Text (39):
To assess the importance of the heparin binding activity of PF4 in the inhibition of endothelial cell proliferation, cells were incubated in media containing or lacking 5 units/ml heparin. The presence of heparin stimulated proliferation of these cells during the three day incubation of this experiment. rPF4 significantly inhibited both control (100%) and heparin stimulated (45%) endothelial cell growth (Table 1).

Detailed Description Text (42):
A mutant of PF4 was created by converting the four lysine residues at the carboxy terminus of PF4 to two Gln-Glu couplets as disclosed above. This protein apparently retains the alpha-helical secondary structure (FIG. 4) for this region of the molecule with the concurrent loss of heparin binding activity.

Detailed Description Text (43):
The protein was reactive with polyclonal antibodies to native PF4 and was determined to possess the appropriate modifications by amino acid analysis. Significantly, the purified mutant protein lacked heparin-binding activity in the Factor Xa inhibition assay.

Detailed Description Text (48):
Purified rPF4-241 was tested for its ability to inhibit capillary growth in the chicken chorioallantoic membrane (CAM) assay. Even at the lowest concentrations tested (1.25 nmol/disc) rPF4-241 extensively inhibited angiogenesis in the CAM

system (FIG. 5). This inhibition was even more effective than that caused by equal concentrations of native rPF4 as suggested by larger avascular zones on the membrane. The inhibitory effect of rPF4-241 was not reversed by heparin.

Detailed Description Text (52):
These results are remarkable in that previous theories of PF4 inhibition of angiogenesis assumed that the PF4 effects were due to heparin binding. We have designed a protein, retaining most of the structural features of native PF4 but lacking detectable heparin binding activity, which may be more active than native PF4 in inhibiting angiogenesis in vivo and endothelial cell proliferation in vitro. Additionally, the mutant we have designed would not be expected to interfere with heparin anticoagulant therapy.

Detailed Description Text (59):
It has been shown that proteins of identified structure and function may be constructed by changing the amino acid sequence if such changes do not significantly alter the protein secondary structure (Kaiser, E. T., and F. J. Kezdy [1984] Science 223:249-255). The subject invention includes other mutants or fragments of the PF4 sequences depicted herein which lack affinity for heparin and exhibit substantially the same or higher angiostatic activity. A preferred region for modification is the lysine rich region near the carboxy terminus corresponding to the heparin binding domain (residues 60-70). As a general rule, amino acids 60 through 70 cannot be eliminated. Also, as a general rule, it is necessary to have at least one charged residue between positions 60 and 70. Maintenance of an amphipathic .alpha.-helix in this region does not seem to be necessary, however, an amphipathic structure may be preferable. Thus, the subject invention includes mutants of the amino acid sequences depicted herein which do not alter the protein secondary structure, or if the structure is altered, the biological activity is retained. In particular it should be understood that conservative substitutions of amino acids may be made. For example, amino acids may be placed in the following classes: basic, hydrophobic, acidic, polar, and amide. Substitutions whereby an amino acid of one class is replaced with another amino acid of the same type fall within the scope of the subject invention so long as the substitution does not materially alter the biological activity of the compound. Table 2 provides a listing of examples of amino acids belonging to each class.

Detailed Description Text (64):
Although most of the resulting compounds still exhibit biological activity in the CAM and HUVEC assays, they do not bind heparin. rPF4-302, which does not exhibit significant activity in either the CAM or the HUVEC assay, has no charged amino acid residues between residues 60 and 70. rPF4-231, which also does not exhibit significant biological activity, terminates at amino acid number 60. If a person skilled in the art wished to investigate the biological activity of other rPF4 mutants, it would now be a straightforward procedure to make the desired mutations and test the resulting peptides for activity. Using the teachings of this document, the researcher could prepare and readily test peptides which could be expected to have the desired properties. For example, the amino acid substitutions just described for the full length rPF4 molecule can also be made with the C-13 and C-41 fragments which are described above.

Detailed Description Text (108):
Disorders of the skin can be treated intralesionally, wherein formulations and dose will depend on the method of administration and on the size and severity of the lesion to be treated. Preferred methods include intradermal and subcutaneous injection. Patients may be capable of self-administration. Preferred dosages are 0.05 to 5 mg rPF4 per dose (0.7 to 70 mg/kg) contained within a volume of 0.1 to 1 ml. Multiple injections into large lesions may be possible, and several lesions on the skin of a single patient may be treated at one time. The schedule for administration can be the same as that described above for the treatment of brain tumors. Formulations designed for sustained release will reduce the frequency of

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administration. Patients can be treated as out- or in-patients, as their health permits.

Detailed Description Text (112):
A dosage is defined as a single dose administered as a bolus injection or intravenous infusion; or the compound can be administered to the patient as an intravenous infusion over a period of a day; alternatively, the compound can be administered in several bolus injections interrupted by periods of time such that the dose is delivered over the course of a 24 hour period. The most preferred method of treatement is to administer the compound to the patient in one injection or infusion per day.

Detailed Description Paragraph Table (1):
TABLE 1 _____ Attenuation of rPF4 inhibition of endothelial cell growth by heparin. rPF4 % Addition -- 50 mcg/ml Inhibition.sup.a _____ -- 14.4 .+-. 2.5 .sup.b 6.0 .+-. 0.6 .about.100 5 u/ml heparin 18.9 .+-. 1.2 .sup.b 14.0 .+-. 0.4 45 _____ .sup.a Based on seeding of 8 .times. 10.sup.4 cells/well .sup.b Significantly different from appropriate control (p < 0.005)

Other Reference Publication (1):
Folkman, J. et al. (1983) "The role of heparin in angiogenesis" Ciba Found. Symp. 100:132-149.

Other Reference Publication (9):
Maione, T.E. et al. (1991) "Inhibition of Tumor Growth in Mice by an Analogue of Platelet Factor 4 That Lacks Affinity for Heparin and Retains Potent Angiostatic Activity" Cancer Research 51:2077-2083.

L7: Entry 207 of 228 File: USPT Jun 23, 1998

DOCUMENT-IDENTIFIER: US 5770623 A
**** See image for Certificate of Correction ****
TITLE: Argine antagonists for inhibition of systemic hypotension associated with nitric oxide production or endothelial derived relaxing factor

Detailed Description Text (3):
Endothelial cells--MBEC's were isolated from murine brain microvessels and cultured on gelatin-coated tissue culture dishes in DME/F12 media supplemented with 2% PPPHS, 5% FBS (Hyolone), 50 .mu.g/ml ECGF (Biomed Tech), and 10 U/ml heparin (Sigma) as previously described (Belloni et al. 1989). The endothelial derivation of MBEC's was determined by the presence of a non-thrombogenic surface to platelets and immunofluorescent staining for Factor VIII related antigen. MBEC's were used between passage 6-9 for all experiments.

Detailed Description Text (35):
FIG. 13 depicts inhibition by NMMA of histamine-induced nitrite release from the isolated coronary perfused guinea pig heart and its restoration by L-arginine. Hearts were perfused at constant pressure (40 cm H.sub.2 O) with Krebs-Henseleit buffer containing the thromboxane A2 analog (U-46619, 86 nM) to induce coronary vasoconstriction. Histamine was administered as a rapid bolus injection into the aorta and net nitrite release during the subsequent 2.5 minutes was determined. Bars represent mean values.+-.SEM (n=4-6). Not shown here is that histamine elicits a dose-dependent increase in coronary flow (vasodilation) which is attenuated by L-NMA, but restored by addition of excess L-arginine. Thus, it appears that NO synthesis from L-arginine mediates, at least in part, histamine-induced coronary artery vasodilation in the guinea pig heart.

Detailed Description Text (62):
The response of the dog to TNF and ET is similar to that observed in humans. In clinical trials in which TNF was administered to cancer patients, hypotension is the dose-limiting toxicity which restricts the dose of TNF which can be administered. As observed in the patient, the time of onset and severity of hypotension is variable in the dog. The administration of ET to the dog is associated with a more severe and uncontrollable form of hypotension than a bolus injection of TNF. This may be due to the fact that TNF has a short half-life in circulation (5 minutes), however, it is continually produced by endogenous sources after administration of ET. This may lead to an increased inductive drive to produce larger amounts of NO in response to ET as compared to TNF. This hypothesis is confirmed by the fact that lower doses of NMMA were required to reverse TNF-induced shock as compared to ET-induced shock.

CLAIMS:

25. The method of claim 1, 2, 3, 4, 5, 6, 7, 10, 11 or 12 wherein the administering is intraperitoneal, intramuscular, intradermal or topical.

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L13: Entry 64 of 107 File: USOC Apr 11, 1967

DOCUMENT-IDENTIFIER: US 3313291 A
TITLE: Apparatus for the injection of radioopaque liquid in angiography

Title (1):
Apparatus for the injection of radioopaque liquid in angiography

OCR Scanned Text (1):
April 11, 1967 T. R. MARSHALL 3,313,291 APPARATUS FOR THE INJECTION OF RADIO-OPAQUE LIQUID IN ANGIOGRAPHY Filed Nov. 6, 1963 2 Sheets-Sheet I C', C) k LO (D cv (o co Clil CD 0) CQ iF) cli Lo LO co LO fn 0 co LO LO GO a) CD K) U') LO T ri) LO C\i (D 'D 0 LO OD CO L(-)- coi I N V E N T O R . K) THO MAS R. MAR SHA LL C\i BY ATTORNEY

OCR Scanned Text (2):
April 11, 1967 T. R. MARSHALL 3,313,291 APPARATUS FOR THE INJECTION OF RADIO-OPAQUE LIQUID IN ANGIOGRAPHY Filed Nov. 6, 1963 2 Sheets-Sheet 2 66 65 64 72 62 76 6 6 7 3 7 5- - - - - - - - 5 6 /1 18 28 6 3 Tr 74 29 23-,\ 22 3 0 F 5 0 5 e . 3 8 9 L8 2 1 14 5 5 5 - - - " - - 5 6 76 7 5 78 3 1 3 8 19 28 18 29 30 , 3 7 ,,-2 8 53 54 57 INVE NTO R. 14 THOMAS R. MARSHALL BY

OCR Scanned Text (3):
United States Patent Office 31313,291 3,313,291 APPARATUS FOR THE INJECTION OF RADIO. OPAQUE LIQUID IN ANGIOGRAPHY Thornas R. Marshall, Louisville, Ky., assignor to Sigma. motor, Inc., village of Mddleport, N.Y., a corpora. tion of New York Filed Nov. 6, 1963, Ser. No. 321,884 9 Clahm. (Cl. 128-2) This invention relates to an apparatus for use in angiography and aorto.-raphy. More specifically, this invention relates to an apparatus whereby one or more injections of radio-opaque liq,,iid can be mad.- without the use of a catheter and without reloading the sy@ringe. @In order to obtain a good radiological contrast, it is necessary to utilize a radio-opaque substance in sufficient arnount to reach a certain de.-roe of concentrat,7on in the blood. Such radio- opaque substances are iodine derivatives which absorb X-rays and consequently are often referred to as contrast materials. The injections must be made very rapidly in order that the contrast material ir@ove in the form of a bolus to the desired area. It is thus necessary to use sufficient pressure to overcome the blood pressure in the brachial artery or other site of injection so as to move a.-ainst the flow of blood to the desired area of the vascular system. It has been found that in ma@ly instances it is necessary to utilize as hi,@h as 400 p.s.i. inj@ction pressure in order to insure that a sufficient quantity of contrast material reaches the desired area in sufficient conceqtration for radiolo.-ical examination. In an article by T. R. Marshall and J. T. Lin.- in Radiolo.-Y, vol. 80, No. 2, pp. 258-260, February 1963, direct percutaneous non- catheter left and right brachiolangio,@raphy was described, wherein the injection site -@vas below the arterial network around the eblow. In this techn-lque, the injection site is in the antecubital fossa. In other instances, injections can be made in the femoral artery depending on the area selected for radiolo.-ical examination. In the development of these techniques it has been found necessary in many instanccs to make multiple injections within a relatively short per@.od of time. A recurrina problem with these procedures is the removal of air froin the contrast inaterial prior to makino, the injections. It is an object of this invention, therefore, to provide a means whereby r-riultiple injections may be given to the sar@ie patient witho-at reloading the syrin.@e.

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Another object of this invention is the pron,ision of a means whereby entrapped air ii the contrast material is remcvved from the syrin,@e prior to makin.- the in- jection. Still another object of this invention is the provision of a-,i apparatus capable of injectin- materials at pressures up to and exceedin.- 800 p.s.i. which is economical and of simple constniction. Still a-.qother object of this invention is the provision of an apparatus whereby the operation of the seriograph and the X-ray apparatus is sync-hronized with the in- jection. Still other and further objects will occur to those skilled in the ar-t from a review of the drawin,,s and the detailed description which follows. Referrin- now to the drawings: FIG. 1 is a side elevation of r@iy injection device. FIG. 2 is an end view taken along lines 2-2 of FIG. 1. FIG. 3 is a vertical cross-sectional view taken along lines 3-3 of FIG. 1. @FIG. 4 is a vertical cross-sectional view taken alon,a lines 4--4 of FIG. 1. FIG. 5 is a fra.amentary horizontal section of my Patented Apr. 11, 1967 2 device which ilIListrates the relation of the plunger assembly to the movable stop inember and particularly to the switching mechanism durin- a stroke of said plun,-er. F-IG. 6 is a side elevational@view partially in section, illustrating the relation of the mova:ble stop mem-bers relative to the plunger shaft assembly and the piston rod assembly. The apparatus of this invention comprises a frame ,-% @,hich includes a front plate 1, a first transverse plate 10 2, a second transverse plate 3, and a rear plate 4. The front plate and the second transverse plate are connected to-ether by side rail members 5 and 8 in which the head of the rail member 5 is on the rear of the second transverse plate 3, and which is secured to the 15 front of the front plate I by nut 6 in a similar manner. The head 10 of rail member 8 is disposed beyond second transverse plate 3 and is secured by nut 9 to the front plate. A third rail member 11 runs from the first transverse plate 2 to the front plate 1 and is secured thereto 20 by means of nut 12. Additionally, the front plate is secured at the bottoin to bottom plate 13 wh;ch runs the length of the apparatus to rear plate 4. Secured to the bottom plate is foot member 14 which disposes the entire apparatus at a sli.-ht an,- le from the horizontal sur- 25 face on which it rests. Therefore, the front of the apparatus is sli.-ht@ly higher than the rear of the apparatus for purposes which will be hereinafter set forth. As will be noted by examination of FIGS. 2 and 3, the front plat-, 1 and the first transverse plate 2 contain cradling 30 slots in the center for provision of the syringe barrel and nozzle 18 and 19, respectively. Tbus, slot 15 in the front plate IL is comparatively narrow so that nozzle 19 projects therethrough. Slot 16 in first transverse plate 2 is wider and is arcuate in shape at the bottom for the 35 provis;on of barrel 13 of the syringe. Projectin- from nozzle 19 into the syrin.-e barrel 18 (see FIG. 5) is the tubular member 20 which has an orifice 21 on its bottorn surface. The outlet orifice 22 thus communicates between the orifice ZIL with the intemal surface of the 40 syring,- barrel. The tubular member 20 terminates on the outside with a threaded member 23 for provision of a couplin.- 24 for hose 25 to which a needle may be attached by conventional coupling means. inear the front of the syringe barrel 18 is a free space 26 which is 45 bounded to the rear by annular shoulder 27 which acts to stop tli-- stroke of plu@iger head 28. Thus, it will be seeri that due to the an.-Ular disposition of the syringe barrel 18 anrl the free space 26, any air which is in the syrin,-e will rise to the top and thus co-i-nmunicate by 50 Means of otitlet orifice 79 of the needle valve 75. Thus, by manipulation of kriob 76 the valve shaft 77 may be oper,--d to a'ilow any entrapped air to be removed through valve openin- 78. In the event that all of the air is not rernoved, th'ere remains about 30 cc. of liquid 55 in the syrin,-e in the free space 26 and, due to the lighter density of the air, this rises to the top and is not injected throu- ,h orifice 21 through tubular rnember 20 to the outlet orifice 22, thus eliminating any appreciable danger of in@ecting air into the patient's vascular system. 60 Slidably positioned in the syrin-,e barrel 18 is the plunger assembly, includin- plun.-er head 28, plunger , ',rk-e-d with calibrations 30i and shaft 29, - ,vhich i m which terminates with a circular flan,-e 3,1 at the end of shaft 29. It will be noted that, due, to the centrauy 65 disposed cradling slots in the front and first transverse plates I and 2, the entire syrin.-e may be easily removed from the apparatus to be cleaned and sterilized. The plun,@er assembly is driven by a pneumatic cylinder 70 32 which is secured at the rear to

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the rear plate 4 by cylinder housing 33, and at the front to the second transverse plate 3 by cylinder housin.,- 34. Support rails 35

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and 36 connected to transverse plate 3 and rear plate 4 support the cylinder in operative relation so that the piston rod 37 which terminates in a circular flange 38 is in abutting relation with flan,-e 31 of the plunger shaft. Connected throu.-h cylinder - housin@ 33 is the air inlet connection 39 terminating in nipple 40 to which air line 41 is attached. Air line 41 is connected to a tog@.le valve of standard construction 4,2 whii@,h, in turn, is connected to air line 43 to the gas cylinder 44. The flow of gas from the cylinder is controlled by hand valve 45 throu.@h reducing valve 46 to high pressure gauge 47 and to low pressure gau.-e 48. Thus, it is possible to reduce the pressiire of the gas coming froni the cylinder from about 1800 p.s.i.g. to 0 through the use of reducin- valve 46. Normally, @as pressures in the range of 80 to 100 p.s.i. are used with the apparatus of this invention. Therefore, by manipulation of to---gle valve 42, the piston rod 37 is extended, thus driving the plun,@er shaft 29 by reason of the abuttin.-relationship of the plunger shaft flan,-e 31 with the,, piston roctflan,-e 38. In the particular embodiment shown, the area of the piston head 49 in the cylinder 32 is ap@proximately four times the area of the plun.-er head 28, therefore, allowing for a mechanical advanta,-e of about 4 to 1. In this manner, with a gas pressure of about 100 p.s.i. the contrast material is ejected from the syrin-,e at a pressure of about 400 p.s.i. The stroke of the piston and plunger assembly is limited by means of movable stop 50 which consists of a metal block assembly mounted on rails 5 and 8, respectively, and which contains a travelin.@ nut 51 at the bottom. The block portion of the movable stop 50 contains a central openin.- 52 which is large enou.ah to accommodate the flano,e portions 31 and 33 of the piston and plunger assemblies. The block portion contains a front and rear transverse slot 53 and 54 into, which stop plates 55 and 56 may be slidably positioned. Projectin- through the traveling nut portion 51 is a worm shaft 57 Nvhich is journaled in collars 58 and 59 of the second transverse plate and the rear plate, respectively, and which is connected to a crank member 60 and crank handle 61. It is, therefore, possible by manipulation of the crank to move the entire movable stop assembly axially in either direction along the side rails 5 and 8 of the frame. Referring now to FIGS. 1 and 5, the switching mechanism contained in housing 65 consists of a stop plate 62 which is adapted to slidably fit into transverse slots 53 or 54 of the movable stop assembly 50. On the back portioii of the stop plate 62 is a depression 63. Attached to stgp plate 62 is a pair of -,Uide rods 64 connected by connect-in.@ member 81, upon which housing 65 is slidably positioned, and which is secured in a particular position by set screw 66. Below the @uide rod 64 and extending through the stop plate 62 is a slidable cam shaft 67 which is biased a,-ainst sprin.@ member 80 and which has an annular restricted portion 68 and a cam surface 69. The cam follower 70 is supported on bracket 71 so as to open switch 72 when the follower is in position over the restricted portion 68 of the cam shaft. Contact of the cam follower 70 with the cam surface 69 closes switch 72 arid thus actuates the serio,-raph and X-ray apparatus. The striking plate 73 is located at the end of the slidable cam shaft 67 and contains a pointer 74 at its lowermost end so that the apparatus may be positioned at any position along the calibrated plunger shaft 29. Upon contact of the flan.-e 3.t of the plunger shaft Nvith the striking plate 73, the switch 72 is closed by reason of the contact of the cam follower 70 with the cam surface 69, thus energizing the seriograph and X-ray apparatus to produce inultiple exposures. It will be noted in the embodiment illustrated in FIG. 5 that the striking plate 73 has been set to be contacted 3,313,291 4 by the flange 31 of the plunger shaft after about 10 cc. of fluid has been injected. In other words, the plunger will have moved from its position to the point indicated by the pointer 74 prior to the closing of switch 72 to actuate the seriograph. This offers certain advantages in that it is sometimes desirable to start the exposure an instant or two after the initial injection to enable the bolus of injectable material to reach the desired area of the vascular system. Thus, for example, if the injection were in the 10 brachial artery, it would require more time for the fluid to reach the

carotid ar-tery than it would to reach the area of the subclavian artery. Thus, with the movable switching arrangement whereby the entire housin.- can be moved to actuate the switch at any des;red point after injection 15 of any desired amount of cohtrast material, it is possible for 'Lhe operator to have precise control over the manner o'L exposure required for a particular radiological examination. It will be noted that the striking plate 73 fits into the recess 63 of stop plate 62 when the plunger assembly 20 has gone the limited stroke. Opei-atioil In the operation of the device, it is first nece-,sary to load the previously sterili@- ,ed syringe. 'rhis is accom- 25 plished by placing the flange members 31 and 38 into abutment and thereafter moving the crank to place the movable stop 50 so that the two flange members are located between the first and second transverse slots 1;3 and 54, respectively, This is best illustrated in Vi6, 6. 30 Thereafter, the stop plates 55 and 56 are positioned into the transverse slots. The crank is then moved so as to force the plunger head 28 fonvard to annular shoulder 27. The needle attached to tube 25 is inserted into the contrast material and the crank handle 61 is then turned 35 in the other direction to move th-@ plunger assembly toward the rear and thus draw conttast matetial into the barrel 18 of the syrin,-C. Normally, the syrin,-e is loaded so the syringe contains about 35 cc. material more thall is required for a particular series of injections. The 40 crank handle 61 is then turned in the other direction after the knob 76 of the valve stem 77 is manipulated to open valve opening 78. The plunger assembly is moved forward until contrast material is seen to be coming out of valve opening 78. Tliereafter, the knob 76 is tumed to 45 seat valve stem 77 on seat valve not shown. Stop plate 56 is then removed and the movable stop 50 is moved until stop plate 55 registers upon the calibration desired for the injection. It is possible to load the syringe by the use of onlv one 5(transverse slot and one slidable plate in the movable stop 50. Assuming this slot to be 54 and the plate to be Sj' as illustrated in FIG. 6, the abutting flan-es 31 and 38 can be moved forwardly to expel air from the syringe. Thereafter the plate 56 is removed and stop 50 is moved 55 forwardly so that slot 54 is in the position shown in FIG. 5. Plate 56 is then inserted in slot 54 and stop 50 is moved rearwardly to load the syringe. The plate 56 is removed and the stop 50 is moved rearwardly to the position shown in FIG. 6 and the plate 56 is reinserted. The 60 stop 50 is then moved forwardly so that plate 56 pushes the plunger flange 31 and the piston rod flan,-e 38 forwardly until liquid is expelled throu.-h needle valve 75. The needle valve is then closed and the plate 56 is a,-ain rernoved and the entire stop 50 is moved forwardly to the 65 point on the calibrated shaft 50 desired for an injection. Plate 56 is inserted into slot 54 and the apparatus is ready for the first inj;ection. It will be noted that, due to the slight angle of the syringe barrel, due to the foot 14 attached to the bottom plate 13, air having a lower density 70 than the contrast material is thus concentrated in the upper end of the syringe barrel or area 26. Thereafter, by moving the plunger head forward, all the air is removed throu.-h the needle valve 75 prior to makin.a the first injection. As a safety factor, the injectable material 75 leaves via orifice 21 and tube 22 which is located in the

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5 lower portion of the free space 26; therefore, in the event that any entrapped air is still within the syrin.-e it will be concentrated at the top of free space 26 and thus wifl not be injected into the patient. After the stop plate 55 has been accurately placed at the desired point alon- the calibrated shaft, the gas valve 45 is open and reducing valve 46 is set so that the pressure re@gistering on -auge 49 is about 100 pounds. The needle is then inserted into the artery of the patient. Thereafter, the tog.-le valve 42 is opened and the pressurized gas forces the piston within cylinder 32 forward so that by means of the abutting relationship of piston fla.i.-e 38 and plun,-er RaD,-e 31, the plun.-er shaft 30 and plunger head 28 is pushed fonvard until stopped by stop plate 55. Thus, an injection of any pre-detenni-ied size may be made. The toggle valve may be closed at will so that the exhaust pressure orifice is opened sorne time after the injection is made, so as not to fri.-bten the patient. Should it be desired to make another injection, it is merely n@-cessary to move the movable stop 50 by manipulation of crank 60 to

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another point on the calibrated shaft and thereafter open to,-,-le valve 42 to make another injection. As previously indicated, it is possible to use stop plate 62 rather than stop plate 55 and to set the housing 65 at any desired point along .rod members 64. Therefore, the striking plate 73 can be set so as to be contacted after initial iniertion of 15 cc. of material has been made, the stop plate 62 servin.to stop the full stroke of the plun.-er i@l the manner previously indicated. It is thus possible to make a series of injections within a matter of seconds, each injection bein.- of predetermined size and to synchronize the seriograph and X-ray apparatus to start the exposures at any pre- determined point durin.- the course of the injection. Many modifications will appear to those skilled in the art from the l'Ore.-oing detailed description, which is intended to be illustrative and not Emiting, except so as to be commensurate in scope with the appended claims. What is claimed is: 1. A power-driven medical apparatus, adapted for use in percutaneous non- catheter angio-.raphy, which comprises; (a) a frame; (b) a diagnostic medical syrin.ae rnounted on said frame and including: (i) a barrel having an oiitlet orifice and includ- ina a plunger assembly slidably mounted for axial reciprocation therein; (ii) said plun.-er assembly comprisin.- a head portion and a shaft in which one end of said shaft is connected to said head portion, and the other end of the shaft extends outside of said barrel; a cylinder including a piston assembly slidably mounted fo.r axial reciprocation in said cylinder and a .@as orifice; (i) said piston assembly including a head portion and a rod in which the rod is connected to said head portion at one end wil,h the free end extending outside of said cylinder, said free end being positioned in operative relation with the shaft of said plunger assembly to drive same; (d) a source of conipressed gas connected to said -as orifice and valve means for controllin.- the flow'of gas to said orifice; aid (e) a movable stop mounted for axial movement on said frarne to physically stop the full stroke of the piston rod ard plun,cer asseiiibly, so that by movement of said stop, sequential injections can be made -without reloading the syringe. 2. A power-driven medical apparatus, adapted fcir use in percutaneous non-catheter angiography, which comprises; (a) a frame; 3,313,291 6 (b) a diagnostic medical syringe mounted on said frame and including; (i) a barrel having an outlet orifice and containing a plunger assembly slidably mounted for 5 axial reciprocation therein, (ii) said plunger assembly comprisin@ a he-ad portion and a shaft in which one end of said shaft is connected to said head portion and the other end of the shaft extends outside of 10 said barrel; (c) a cylinder, including a piston assembly slidably mounted for axial reciprocation in said cylinder and a gas orifice, (i) said piston assembly including a head portion 15 and a rod in which the rod is connected -to said head portion at one end with the free end extending outside of said cylinder, said free end being positioned in operative relation with the shaft of said plunger assembly to drive same; 20 (d) a source of compressed igas connected to said -as orifice and valve means for controlling the flow of gas to said gas orifice; (e) a calibrated means to @measure the amount of liquid in said syrin,@e; and 25 (f) a movable stop mounted for axial movement on said frame in visual relation to said calibrated means to physically stop the full stroke of the piston rod and plunger assernbly so that by movement of said stop, sequential injections of predetermined size can 30 be made without reloading the syringe. 3. A power-driven medical apparatus adapted for use in percutancous non-catheter an.-io.@raphy, which comprises; @(a) a frame, said frame comprising a front pl@ate mem- 35 ber and a back plate memb,-r and side rail members; (b) a dia-nostic medical syrin.-c mounted on said frame and including: (i) a barrel having an outlet (yrifice and contain- in.- a plunger assembly slidably mounted for 40 axial reciprocation therein, (ii) said plun,@er assembly comprising a head portion and a shaft in which one end of said shaft is connected to said head portion, and the other end of the shaft extends outside of said barrel; 45 (c) a cylinder includin.- a piston assembly slidably mounted for axial reciprocation in said cylinder and a .-as ori-'tice, (i) said piston assembly, includin@ ahead portion and a rod in which the rod is connected to said 50 head portion at one end with the free end ex-tendin.- outside of said cylinder, said free e,,id bein- positioned in operative relation with the shaft of said plun.-er assembly to drive sarne; .(d) a source of com@pressed aas cgnnected to said @as 55 orifice and valve means for controlling

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the flow of .@as to said orifice; and (e) a movable stop mounted on said rail members for iaxial movement thereon, to physically stop the ftill stroke of the piston rod and pILirger assembly, so that 60 by movement of said stop, sequential injections can be made withollt Teloading the syrin@C. 4. A po-wer-driven medical appatatus adapted for use in . percutancous non-catheter angio.-raphy, which comprises; 65 (a) a frame, s-aid frame comprising a front plate mem- ber, an intermediate transverse plate member, and a rear plate member i@i which said front plate member and said intermediate plate member contain cradlinslots; 70 (b) a dia,,anostic medical syrin,-e detachably cradled in said slots of said front and intermediate transverse plate members, which comprises; (i) a barrel havin- an outlet orifice and contai-@iin.- a plun.-er asse'mbly slidably mounted foT axial 75 reciprocation therein,

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7 (ii) said plunger assembly comprisin@ a head portion and a shaft in which one end of said shaft is connected to said head portion, and the other end of the shaft extends oiitside of said barrel; (c) a cylinder includin.- a piston assembly slidably mounted for axial reciprocation in said cylinder and a gas orifice, (i) said piston assembly, includin- a head por-tion and a rod in which the rod is connected to said head portic>n at one end, with the free end extendin,- outside of said cylinder,. said free end being positioned in operative relation with the shaft of said plun-er assembly to drive same; (d) a source of compressed -as connect-@d to said -as orifice and valve means for controllin.- the flow of gas to said orifice; and (e) a movable stop inounted for axial movement on said frame to physically stop the full stroke of the piston rod and plunger assembly, so that by movement of said stop, sequential injections can be made without reloading the syrin,@e. 5. A pressure medical injector adapted for use for injectin.,@ radio-opaque liquid in the technique of an.-iography, which comprises; (a) a frame, (b) a diagnostic medical syrin.-e, including @a barrel havin.- a plun.- er assembly slidably molinted therein for axial reciprocation, (i) said barrel bein.- mounted in said frame so that the front portion of the barrel is sli.-htly elevated over the rear pc)rtion of the barrel, (ii) said bar-rel having an escape valve mounted on the top and at the front thereof, which communicates with the inside of the barrel, said barrel havin- an outlet orifice in the front thereof, said orifice bein.- located in the IOWCT portion of the front of said barrel, (iv) said barrel being constricted on its intemal surface near the front end, so as to physically prevent the plun@.er assembly going fuli stroke; and (e) power means adapted to propel the plun.@,-r axially, whereby liquid contained in said barrel may be ejected undet pressure. 6. A power driven medical apparatus as defined in claini 1, in which: (a) said free end of said plun.-er shaft and said free end of said piston rod each contain flan.-e members, adapted to fit in abuttin.- relation; (b) said movable stop comprises a block havin,.- an opening in the center throuah which the piston rod and the shaft of the plun.-er can move and which contains: (1) two transverse slots, and :(2) two plates slidably positioned in said slots to enga,-e witb the flan.-e members of said plun.-er shaft and said piston rod; and (c) means for movin.- said block axially in either di- 3,313,291 8 rection so as to extend the shaft of said plun.-er and retract the rod of said pistgn to load the syrin.-e and thereafter to move the en@lire stop forward to expel air from the syringe. 5 7. A power driven medical apparatus as defined in claim 1, in which: (a) said movable stop contains an openin.- in the center throu.-h which the piston rod and the shaft of the plunger can move and which contains at least one 10 transverse slot; (b) the further combination therewith of a switch and a switch actuating mechanism; (1) said switch actuating mechanism comprising; (a) a plate slidably positioned in said slot; 15 (b) an adjustable cam shaft extending through said plate, said cam shaft being responsive to the movement of said piston rod and plun,@er shaft; and (c) a cam follower mounted in operative 20 relat;on with said switch and said cam shaft; (d) so that movement of said piston rod and plunger shaft moves said cam shaft and said cam follower follows the surface of 25 said cam shaft to actuate said switch. S. A power driven medical apparatus as defined in claim 1, in which: (a) said movable stop comprises a block havin.- an openin.- in the center throu,@h which the

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piston rod 30 and the shalt of the plun.-er can move, (1) said block containing a transverse slot; (b) a plate slidably positioned in said slot and engageable with said piston rod and said shaft of said plunger to limit the stroke of each; and 35 (e) means for movin,@ said block axially in either di- rection along said frame. 9. A pressure medical injector as defined in claim 5, in which: (a) said outlet orifice comprises a hollow tubular mem- 40 ber which projects into said barrel, (1) said tubular member being closed at the end located inside the barrel and containing an orifice near the closed end and on the underside 45 thereof.

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L1: Entry 18 of 20 File: USPT Mar 11, 2003

DOCUMENT-IDENTIFIER: US 6530900 B1
TITLE: Drug delivery device

Brief Summary Text (2):
A wide range of subcutaneous drug delivery devices are known in which a drug is stored in an expandable-contractible reservoir. In such devices, the drug is delivered from the reservoir by forcing the reservoir to contract. (The term "subcutaneous" as used herein includes subcutaneous, intradermal and intravenous.)

Brief Summary Text (7):
For devices which employ a needle to penetrate the skin there is a danger that after use the device may accidentally infect the patient or others if not properly disposed of. WO 95/13838 discloses an intradermal device of this type having a displaceable cover which is moved between a first position in which the needle is retracted before use and a second position in which the needle is exposed during use. Removal of the device from the skin causes the cover to return to the first position in which the needle is again retracted before disposal. However, this device does not include a locking mechanism in the assembly for locking the device prior to use to minimize accidental contact with the needle and/or accidental actuation of the device that may occur during shipping and/or storage.

Brief Summary Text (55):
Further, in a preferred embodiment, the subcutaneous drug delivery device includes a pressure sensitive mechanism for preventing a rapid injection of a drug to a user. For example, the pressure sensitive mechanism can include a switch that forms a part of the electrical circuit which controls the power supply to a gas generating portion of the drug delivery device. The switch can include different preferred components to complete the circuit, such as one including a conductive membrane and a conductive lever, or alternatively, electrodes and a droplet of mercury. The electrical circuit is completed as long as the pressure in the gas generating portion is less than the pressure within a chamber.

Detailed Description Text (94):
In another preferred embodiment, the subcutaneous drug delivery device can include a pressure sensitive mechanism, such as in FIG. 37A, for preventing bolus delivery or rapid injection of a drug into the user. A switch 300 can prevent a rapid injection of drug to a user as a result of an increase in pressure in the drug delivery device. The switch 300 can help to avoid an increase in pressure within the drug delivery device caused by blockage of the needle. The switch 300 can form part of a circuit 250, as shown in FIG. 32A, which controls the power supply to a gas generating portion of the drug delivery device.

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L1: Entry 20 of 20 File: USPT Apr 2, 2002

DOCUMENT-IDENTIFIER: US 6365372 B1
TITLE: SNF2 related CBP activator protein (SRCAP)

Detailed Description Text (52):
The polypeptide, polynucleotide, and antibody compositions of the present invention can variously be administered to a mammalian or other vertebrate patient, including humans, for therapeutic purposes. For these purposes, the compositions preferably also comprise a pharmaceutically acceptable carrier or diluent. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The carrier can also contain other pharmaceutically-acceptable excipients for modifying or maintaining the pH, osmolarity, viscosity, clarity, color, sterility, stability, rate of dissolution, or odor of the formulation. Similarly, the carrier may contain still other pharmaceutically-acceptable excipients for modifying or maintaining release or absorption or penetration across the blood-brain barrier. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier that constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Detailed Description Text (56):
The therapeutic or pharmaceutical compositions of the present invention can be administered by any suitable route known in the art including for example intravenous, subcutaneous, intramuscular, transdermal, intrathecal or intracerebral. Administration can be either rapid as by injection or over a period of time as by slow infusion or administration of slow release formulation. For treating tissues in the central nervous system, administration can be by injection or infusion into the cerebrospinal fluid (CSF). When it is intended that the composition be administered to cells in the central nervous system, administration can be with one or more agents capable of promoting penetration of SRCAP across the blood-brain barrier.